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# Outcomes of hospitalisation for right heart failure in pulmonary arterial hypertension

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**ABSTRACT: The aim of this study was to examine the causes and outcomes of hospitalisation in patients with pulmonary arterial hypertension (PAH).**

**205 consecutive hospitalisations occurring between 2000 and 2009 in 90 PAH patients were studied.**

**The leading causes for hospitalisation were right heart failure (RHF; 56%), infection (16%) and bleeding disorders (8%). For patients with RHF, in-hospital mortality was 14% overall, 46% for patients receiving inotropes and 48% for those admitted to the intensive care unit. The predictors for in-hospital mortality were the presence of connective tissue disease (CTD) (OR 4.92), systolic blood pressure <100 mmHg (OR 4.32) and Na ⩽136 mEq·L$^{-1}$ (OR 4.29). Mortality after discharge was 13, 26 and 35% at 3, 6 and 12 months, respectively. World Health Organization functional class prior to admission, renal dysfunction, Charlson comorbidity index, and the presence of CTD were all predictors of mortality after discharge.**

**Hyponatraemia and low systolic blood pressure upon admission and underlying CTD are the main prognostic factors for in-hospital mortality in patients with PAH admitted for RHF. The short-term outcomes after discharge are poor and remarkably worse in patients with underlying CTD or renal impairment. Early recognition of these factors may guide decisions regarding more aggressive therapy, including consideration for lung transplantation.**

**KEYWORDS: Connective tissue diseases, heart failure, hospital mortality, right ventricular dysfunction, scleroderma, systemic**

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Pulmonary arterial hypertension (PAH) remains a disease with high morbidity and mortality rates despite recent advances in therapy and overall improved survival. PAH is usually progressive, with right ventricular dysfunction being the leading cause of death. Patients often require hospitalisation during the course of their disease, typically for bouts of right heart failure (RHF). In addition, complications related to treatment itself, including PAH-specific therapy, anticoagulation and long-standing indwelling catheters, constitute other potential causes of hospitalisation.

In contrast with left heart failure (LHF), the course and outcomes of acute or decompensated RHF have been seldom described [1, 2]. Several features differentiate RHF secondary to severe PAH from LHF and make management of RHF particularly challenging. While aggressive diuresis is usually required in both LHF and RHF, the large increase in transpulmonary gradient due to a fixed resistance in the pulmonary vasculature in PAH complicates the treatment of RHF. In addition, right ventricular–left ventricular interdependence often leads to left ventricular dysfunction with low cardiac output and consequent systemic hypotension in RHF, which may require the use of vasopressor and inotropic agents. These haemodynamic perturbations may be further complicated by decreased myocardial perfusion from compromised coronary flow due to right ventricle overload. Ultimately, these processes can lead to distal organ dysfunction and irreversible haemodynamic collapse.

The causes, clinical burden and outcomes of hospitalisation for RHF have been poorly characterised and their impact on overall clinical course is unknown. Thus our study aimed to analyse the causes, clinical characteristics and outcomes of hospitalisation, as well as prognostic factors for mortality, in a cohort of PAH patients closely followed at a specialised pulmonary hypertension clinic. Some of the results of this study have been previously reported in abstract form [3].

## PATIENTS AND METHODS

### *Patient population*

This study was approved by the Johns Hopkins University Institutional Review Board (Baltimore, MD, USA). Adult patients with PAH evaluated at

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the Johns Hopkins Pulmonary Hypertension Program were prospectively included in the Hopkins Pulmonary Hypertension Registry. Data from hospitalisations occurring at Johns Hopkins Hospital and its affiliate Johns Hopkins Bayview Medical Center from January 2000 to March 2009 were analysed.

The diagnosis of PAH (World Health Organization (WHO) group 1) was established by haemodynamic criteria (mean pulmonary artery pressure $\geqslant$25 mmHg, pulmonary capillary wedge pressure $\leqslant$15 mmHg, and pulmonary vascular resistance (PVR) >3 Wood units) and exclusion of other potential causes of pulmonary hypertension (WHO groups 2–5) [4]. Within WHO group 1, we limited our analysis to patients with idiopathic PAH (IPAH), and anorexigen-induced PAH (AiPAH; *i.e.* PAH associated with drugs/toxins) and connective tissue disease (CTD)-associated PAH, thus excluding other causes of WHO group 1 PAH, such as portopulmonary hypertension, haemoglobinopathies or HIV. The decision to exclude these conditions was based on the high prevalence of comorbidities in these patients that lead to hospitalisation unrelated to PAH. Although comorbid conditions are also common in CTD-PAH, we included these patients because of our long interest in their outcomes [5–8] and the fact that they represent the bulk of referral to our pulmonary hypertension programme. Patients with significant interstitial lung disease as previously defined (total lung capacity <60% or 60–70% with significant interstitial radiological changes) were excluded [6–8].

Electronic records and file charts were reviewed to obtain demographic information, past medical history, findings on admission and at discharge, and information on therapy during hospitalisation and medications prescribed at discharge. The Charlson comorbidity index was calculated from the medical history [9]. Anaemia was defined by haemoglobin <13 $g \cdot dL^{-1}$ for males and <12 $g \cdot dL^{-1}$ for females [10]. The estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the Modified Diet in Renal Disease equation [11]. Hyponatraemia was defined as serum Na $\leqslant$136 $mEq \cdot L^{-1}$ based on previous literature on PAH [5] and LHF [12, 13].

In-hospital mortality was analysed for general and RHF hospitalisations after exclusion of 45 elective admissions in stable patients (*i.e.* patients requiring initiation of treatment, elective surgery, or change of central infusion catheter). Mortality at 3, 6, and 12 months after discharge was analysed for patients with a first hospitalisation due to RHF. The diagnosis of RHF was considered in the presence of symptoms and physical evidence of volume overload (increased dyspnoea and weight gain, peripheral oedema or ascites, increased jugular venous pressure, and audible S3 gallop on auscultation) and inclusion of the diagnosis on the discharge report and/or billing code sheet (acute cor pulmonale, volume overload or RHF). Death after discharge was determined from the hospital records as well as the Social Security Death Index up to September 25, 2009. The latest clinic visit or contact with the patient up to that date was considered as censoring time for living patients. Lung transplantation was considered as a failure event in survival analysis, thus lung transplant recipients were excluded from further analysis after transplantation.

The analysis of risk factors for in-hospital mortality included demographics, underlying PAH disease, Charlson index, WHO functional class (FC) at the latest outpatient assessment, physical signs, laboratory parameters on admission, and previous hospitalisation for RHF. Risk factors for mortality after discharge included all factors mentioned above, in addition to laboratory parameters at discharge.

### Statistical methods

Group comparisons were made using the Chi-squared and Fisher exact tests as appropriate for categorical variables and an upaired t-test or Mann–Whitney test as appropriate for continuous variables. Systolic blood pressure (SBP) was considered for analysis both as a continuous and a dichotomised variable (SBP > or $\leqslant$100 mmHg) [12]. Correlation analyses (Spearman rho) were performed to identify significant correlations between variables considered for regression analysis. The identification of prognostic factors for in-hospital mortality was performed using logistic regression with robust adjustment of the variance for repeated measurements in order to handle patients with multiple hospitalisations [14]. Mortality and readmission after discharge were assessed using the Kaplan–Meier method and Cox proportional hazards models. Risk factors were adjusted for age and underlying PAH type in multivariate analysis. Comparisons between groups were assessed by log-rank test. All computations were performed using Stata statistical software (version 10.1; Stata, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

## RESULTS

### Characteristics of patients and hospitalisations

After the exclusion of 45 admissions for elective causes, 205 hospitalisations in 90 patients were identified. The underlying diagnosis were IPAH (61 hospitalisations; 29.8%), Ai-induced PAH (26; 12.6%), systemic sclerosis (SSc) (113; 55.1%) and CTD not including SSc (five; 2.4%). The most common causes for nonelective admissions were RHF (115; 56.1%), infection (32; 15.6%), bleeding (17; 8.3%), arrhythmia (13; 6.3%) and syncope (12; 5.8%). Among infections, those related to indwelling catheter were the most frequent (14 admissions; 43.8%), followed by pneumonia (seven admissions; 21.9%). Bleeding disorders included gastrointestinal bleeding (seven hospitalisations; 41.2%) and haemoptysis (six; 35.3%). gastrointestinal bleeding occurred exclusively in six patients with scleroderma. Atrial fibrillation on admission was present in a minority of patients (7.3%). Intensive care unit (ICU) hospitalisation was required in 16.1% of hospitalisations, and overall in-hospital mortality was 8.8%.

### Hospitalisations for RHF

115 hospitalisations due to RHF were identified in 61 patients. The characteristics of the patients and hospitalisations, and differences between patients with or without CTD are shown in tables 1 and 2, respectively. Haemodynamic data obtained at the time of PAH diagnosis indicated severe PAH with a mean pulmonary arterial presssure ($\bar{P}_{pa}$) of 49 mmHg, cardiac index (CI) of 2.22 $L \cdot min^{-1} \cdot m^{-2}$ and PVR of 10.8 Wood units. At the time of PAH diagnosis, patients with CTD-PAH had significantly lower $\bar{P}_{pa}$ compared with IPAH/AiPAH patients, but other haemodynamic parameters such as CI or PVR were similar between the two groups. The median time from PAH diagnosis to first RHF admission was 11 months for all patients and not significantly different between the IPAH/AiPAH and CTD-PAH groups.

**TABLE 1** Characteristics of patients admitted with right heart failure (RHF)

| | All | IPAH/AiPAH | CTD-PAH | p-value |
|---|---|---|---|---|
| **Subjects n** | 61 | 22 | 39 | |
| **Age upon first admission yrs** | 55±14 | 46±13 | 60±11 | <0.01 |
| **Female** | 56 (91.8) | 22 (100) | 34 (87.2) | 0.15 |
| **Ethnicity/race Caucasian/Black/Hispanic/Asian/others** | 47/11/2/0/1 | 16/4/1/0/1 | 31/7/1/0/0 | 0.61 |
| **Underlying diagnosis** | | | | NA |
| IPAH | 15 (24.6) | 15 (68.2) | | |
| AiPAH | 7 (11.5) | 7 (31.8) | | |
| SSc | 37 (60.7) | | 37 (94.9) | |
| Diffuse SSc | 3 (8.1) | | | |
| Other CTD | 2 (3.3) | | 2 (5.1) | |
| **Median time since PAH diagnosis to first RHF admission months** | 11.1 (0–25.2) | 13.9 (1–25) | 11 (1–28) | 0.98 |
| **Right heart catheterisation at PAH diagnosis** | | | | |
| $P_{ra}$ mmHg | 10±5 | 10±6 | 10±5 | 0.95 |
| $\bar{P}_{pa}$ mmHg | 49±13 | 55±14 | 45±10 | <0.01 |
| CI L·min$^{-1}$·m$^{-2}$ | 2.22±0.68 | 2.14±0.57 | 2.26±0.73 | 0.54 |
| $P_{pcw}$ mmHg | 10±3 | 10±4 | 10±3 | 0.87 |
| PVR Wood units | 10.8±5.6 | 12±5 | 10±6 | 0.43 |
| **Comorbidities** | | | | |
| Coronary artery disease | 3 (5.1) | 0 | 3 (7.9) | 0.55 |
| Systemic hypertension | 17 (27.9) | 9 (40.9) | 8 (20.5) | 0.14 |
| Diabetes mellitus | 4 (6.6) | 1 (4.5) | 3 (7.7) | 1 |
| Peripheral vascular disease | 9 (14.8) | 0 | 9 (23.1) | 0.02 |
| Cerebrovascular disease | 2 (3.3) | 2 (9) | 0 | 0.13 |
| History of depression | 11 (18.1) | 1 (4.5) | 10 (25.6) | 0.04 |
| **Charlson comorbidity index** | | | | <0.01 |
| 0 | 19 | 19 | 0 | |
| 1 | 20 | 2 | 18 | |
| 2 | 12 | 0 | 12 | |
| ⩾3 | 10 | 1 | 9 | |
| **Status at the end of follow-up n** | | | | <0.01 |
| Alive, not transplanted | 14 (23) | 8 (36.4) | 6 (15.4) | |
| Lung transplant recipients | 5 (8.2) | 5 (22.7) | 0 | |
| Dead | 42 (68.8) | 9 (40.9) | 33 (84.6) | |

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwised indicated. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; AiPAH: anorexigen-induced PAH; SSc: systemic sclerosis; CTD: connective tissue disease; RHF: right heart failure; $P_{ra}$: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CI: cardiac index; $P_{pcw}$: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; NA: not applicable.

In-hospital mortality was 14% overall, and 48, 46 and 100% when ICU admission, use of inotropes/vasopressors or mechanical ventilation were required, respectively. The causes of mortality were progressive RHF in 13 (81.3%), sepsis in two (12.5%), and gastrointestinal bleeding in one (6.2%).

*Demographics*

As shown in table 1, compared with IPAH/AiPAH, patients with CTD-PAH were older, comprised a lower proportion of females, had a higher Charlson comorbidity index and were more likely to have a history of depression, but had similar functional impairment as assessed by the WHO FC. On admission, patients with CTD-PAH demonstrated lower heart rate, and had poorer renal function as assessed by serum creatinine, blood urea nitrogen (BUN) levels or eGFR. Serum pro-brain natriuretic peptide (proBNP) level on admission was available in 41 patients and was higher in the patients with CTD-PAH.

*Hyponatraemia*

Hyponatraemia (Na ⩽136 mEq·L$^{-1}$) on admission was present in 52 (45.2%) patients, and was moderate or severe (Na <130 mEq·L$^{-1}$) in 11 (9.6%). Patients with hyponatraemia compared with those with normal sodium levels had similar age (p=0.20), WHO FC prior to admission (p=0.26) and frequency of renal impairment (52% *versus* 44%; p=0.42), but presented with significantly lower SBP on admission (103 *versus* 120 mmHg; p<0.01), higher heart rate (99 *versus* 91 bpm; p=0.01), and more elevated serum BUN (32 *versus* 24 mg·dL$^{-1}$; p<0.01) and proBNP (11,099 *versus* 5,088 pg·mL$^{-1}$; p=0.04) levels. These patients also had a longer median length of stay (9 *versus* 6 days; p=0.02), more commonly required inotropes (48.1 *versus* 15.9%; p<0.01) or ICU admission (38.5 *versus* 14.3%; p<0.01), and were more likely to die in hospital (23.1 *versus* 6.3%; p=0.01). There was a significant correlation between natraemia and SBP on admission (Spearman rho

**TABLE 2** Characteristics of right heart failure (RHF) hospitalisations

| | RHF hospitalisations | | | |
|---|---|---|---|---|
| | All | Comparison by diagnosis | | |
| | | IPAH/AiPAH | CTD-PAH | p-value |
| **Subjects n** | 115 | 54 | 61 | |
| **Age yrs** | 55±15 | 45±12 | 63±12 | <0.01 |
| **Female** | 106 (92) | 54 (100) | 52 (85.2) | <0.01 |
| **Charlson comorbidity index** | | | | <0.01 |
| <2 | 74 (64.3) | 51 (94.4) | 23 (37.7) | |
| ⩾2 | 41 (35.6) | 3 (5.6) | 38 (62.3) | |
| **WHO FC pre-admission (II/III/IV)** | 22/70/21 | 13/34/7 | 9/36/14 | 0.23 |
| **Admission** | | | | |
| Systolic BP# mmHg | 112±20 | 111±21 | 113±19 | 0.76 |
| Diastolic BP# mmHg | 68±13 | 71±14 | 66±12 | 0.06 |
| Heart rate¶ bpm | 95±16 | 98±17 | 91±14 | 0.02 |
| Atrial fibrillation on ECG¶ | 5 (4.5) | 2 (3.8) | 3 (5.1) | 1 |
| s-creatinine mg·dL$^{-1}$ | 1.31±0.8 | 1.04±0.5 | 1.54±1.0 | <0.01 |
| eGFR+ mL·min$^{-1}$/1.73 m$^2$ | 62±26 | 76±24 | 50±22 | <0.01 |
| eGFR | | | | |
| <60 mL·min$^{-1}$/1.73 m$^2$ | 55 (47.8) | 11 (20.4) | 44 (72.1) | <0.01 |
| <30 mL·min$^{-1}$/1.73 m$^2$ | 14 (12.2) | 3 (5.6) | 11 (18) | 0.05 |
| BUN mg·dL$^{-1}$ | 28±16 | 19±11 | 35±16 | <0.01 |
| Na mEq·mL$^{-1}$ | 136±5 | 136±5 | 137±5 | 0.47 |
| Na ⩽136 mEq·mL$^{-1}$ | 52 (45.2) | 24 (44.4) | 28 (45.9) | 0.87 |
| Haemoglobin g·dL$^{-1}$ | 12.2±2.3 | 12.5±2.2 | 12.0±2.3 | 0.17 |
| Haematocrit % | 38.0±6.2 | 38.8±6.0 | 37.5±6.3 | 0.26 |
| Anaemia | 52 (45.2) | 21 (38.9) | 31 (50.8) | 0.20 |
| ProBNP+ pg·mL$^{-1}$ | 3602 (2082–6897) | 2260 (1705–2968) | 5919.5 (3534–10698) | <0.01 |
| Subjects n | 41 | 17 | 24 | |
| ICU admission | 29 (25.2) | 10 (18.5) | 19 (31.1) | 0.12 |
| Inotropes/vasopressors | 35 (30.4) | 14 (25.9) | 21 (34.4) | 0.32 |
| Mechanical ventilation | 9 (7.8) | 3 (5.6) | 6 (9.8) | 0.50 |
| Weight lost during hospitalisation+ kg | 3.6 (1.6–5.7)++ | 3.5 (1.5–6.1) | 3.9 (1.6–5.3) | 0.96 |
| Length of stay+ days | 7 (4–12) | 6 (3–12) | 8 (4–12) | 0.23 |
| **In-hospital mortality** | | | | |
| All§ | 16 (14.0) | 4 (7.4) | 12 (19.7) | 0.06 |
| ICUƒ | 14 (48.3) | 3 (30) | 11 (57.9) | 0.24 |
| Inotropes/vasopressors## | 16 (45.7) | 4 (28.6) | 12 (57.1) | 0.17 |
| Mechanical ventilation¶¶ | 9 (100) | 3 (100) | 6 (100) | NA |

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise indicated. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; AiPAH: anorexigen-induced PAH; CTD: connective tissue disease; WHO FC: World Health Organization functional class; BP: blood pressure; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; ProBNP: pro-brain natriuretic peptide; ICU: intensive care unit. #: n=112; ¶: n=111; +: comparison using Mann–Whitney test; §: n=115; ƒ: n=29; ##: n=35; ¶¶: n=9; ++: n=91. All percentages refer to episodes of hospitalisation.

0.55; p<0.01). There was no significant correlation between eGFR and natraemia.

*Renal dysfunction*

Renal dysfunction, defined as eGFR<60 mL·min$^{-1}$/1.73 m$^2$, was present on admission in 55 patients (48%); these patients had a longer length of stay (8 *versus* 6 days, p=0.03), required more frequent ICU admission (33 *versus* 13%; p=0.01) or inotropes (40 *versus* 20%; p=0.02), and their in-hospital mortality tended to be higher (20 *versus* 8%, p=0.10).

***Treatment characteristics during hospitalisation for RHF***

On admission, 95 (82.6%) out of the 115 patients admitted with RHF were already receiving PAH-specific therapy: 43 (45.3%) were on monotherapy, and 52 (54.7%) were on combined treatment. The most commonly used drugs were phosphodiesterase-5 inhibitors (PDE5-i) (58 patients) followed by endothelin receptor antagonists (50 patients), and prostanoids (49 patients).

During hospitalisation for RHF, patients received standard treatment based on their status severity and decisions of the attending physician. Inotropes or vasopressors were administered

in 30.4% of patients, with dopamine being the most common drug choice (29.6%), followed by norepinephrine (11.3%). Dopamine was used in combination with other vasoactive drugs in 18 out of 34 patients. Three patients required haemodialysis or haemofiltration. One atrial septostomy was performed in a patient who eventually died during the hospitalisation.

At discharge, loop diuretics were prescribed in 97 patients (98%), with a median (range) dose for furosemide of 160 (5–500) mg per day. Aldosterone antagonists were prescribed in 81.8%, digoxin in 15.1%, calcium channel blockers in 16.5% and angiotensin inhibitors in 12.1%.

### Risk factors for in-hospital mortality after RHF admission

Significant risk factors for in-hospital mortality are shown in table 3. After adjusting for age, the presence of underlying CTD portended an odds ratio for mortality of 4.9 (p=0.03). After adjusting for age and underlying diagnosis, the independent risk factors were SBP <100 mmHg on admission (OR 4.32; p=0.01) and Na ⩽136 mEq·L$^{-1}$ (OR 4.29; p=0.02).

### Outcomes after discharge

Of the 61 patients with a first admission for RHF at our centre, seven died during hospitalisation. Thus, outcomes after discharge where assessed in 54 patients. At discharge, 48 of these patients were on PAH-specific treatment: 25 patients were on monotherapy (10 prostanoids, five endothelin receptor antagonists, seven PDE5-i, and three high-dose calcium channel blockers), and 23 patients on combined therapy. The baseline haemodynamic data of survivors of first RHF admission were not different between the CTD-PAH and IPAH/AiPAH groups (results not shown). In total, 15 patients were receiving intravenous prostacyclin, three subcutaneous treprostinil and one intravenous treprostinil at the time of discharge. The use of intravenous prostacyclin was higher in IPAH/AiPAH: 10 (50%) patients with IPAH/AiPAH were discharged on intravenous prostacyclin compared with only five (14.7%) patients with CTD-PAH (p<0.01). Median survival after discharge for patients with CTD-PAH and IPAH/AiPAH receiving intravenous prostacyclin was 5.3 and 18 months, respectively (p<0.01). However, for those patients on prostacyclin, baseline haemodynamic data were significantly worse in the CTD-PAH compared with the IPAH/AiPAH subgroup $\bar{P}_{pa}$ 54 *versus* 53 mmHg; p=0.85; PVR of 16.5 *versus* 9.6 Wood units; p=0.02; and CI of 1.6 *versus* 2.4 L·min$^{-1}$·m$^{-2}$; p=0.03).

During the first year of follow-up, 18 patients (33%) died, and three patients with IPAH received lung transplantation. The mortality rates at 3, 6 and 12 months were 13, 26 and 35%, respectively (fig. 1a). The causes of death after discharge were RHF (12 patients), sudden cardiac death (one patient), massive haemoptysis (one patient), sepsis (one patient) and unknown (three patients). Only two patients were censored before completing 12 months of follow-up. The median survival since PAH diagnosis was 4.2 yrs for patients with IPAH/AiPAH and 3.1 yrs for patients with CTD-PAH (p=0.03). At the end of follow-up only 15.4% of CTD-PAH patients were alive compared with 59.1% of IPAH/AiPAH patients (p<0.01).

### Risk factors for mortality

Univariable and multivariable analysis for mortality or lung transplantation after discharge are shown in table 4. After adjusting for age and underlying diagnosis, the independent risk factors were WHO FC prior to admission (hazard ratio (HR) 3.58; p<0.01), Charlson comorbidity index ⩾2 (HR 2.98;

**TABLE 3** Risk factors for in-hospital mortality in right heart failure (RHF) hospitalisations

| | Unadjusted OR (95% CI) | p-value | Adjusted for underlying diagnosis and age OR (95% CI) | p-value |
|---|---|---|---|---|
| **Age per year** | 1.0 (0.98–1.03) | 0.67 | NA | |
| **Male *versus* female** | 1.88 (0.46–7.7) | 0.38 | 1.17 (0.32–4.25) | 0.81 |
| **CTD-PAH *versus* IPAH/AiPAH** | 3.1 (1.0–9.35) | 0.05 | 4.92 (1.18–20.6)# | 0.03 |
| **WHO FC pre-admission** | 1.91 (0.75–4.85) | 0.17 | 1.61 (0.63–4.09) | 0.32 |
| **Charlson index ⩾2** | 2.69 (0.97–7.46) | 0.06 | 1.96 (0.68–5.61) | 0.21 |
| **Data on admission** | | | | |
| **Systolic BP per mmHg decrease** | 1.05 (1.02–1.09) | <0.01 | 1.06 (1.02–1.10) | <0.01 |
| **Systolic BP ⩽100 mmHg** | 3.62 (1.18–11.1) | 0.02 | 4.32 (1.37–13.6) | 0.01 |
| **Heart rate per beat** | 1.02 (0.98–1.05) | 0.32 | 1.02 (0.99–1.06) | 0.19 |
| **Haematocrit %** | 0.92 (0.83–1.02) | 0.10 | 0.93 (0.84–1.02) | 0.14 |
| **eGFR <60 mL·min$^{-1}$/1.73 m$^2$** | 2.75 (0.92–8.23) | 0.07 | 2.27 (0.53–9.77) | 0.27 |
| **Na ⩽136 mEq·mL$^{-1}$** | 4.42 (1.36–14.4) | 0.01 | 4.29 (1.29–14.7) | 0.02 |
| **ProBNP pg·mL$^{-1}$ (log transformed)¶** | 65.4 (4.5–946) | <0.01 | NA | |
| **Previous RHF hospitalisation** | 1.54 (0.55–4.34) | 0.41 | 2.66 (0.67–10.5) | 0.16 |
| **Need for inotropes** | 136.2 (7.83–2370) | <0.01 | NA | |
| **Need for mechanical ventilation** | 252.1 (13.34–4764) | <0.01 | NA | |

CTD: connective tissue disease; PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; AiPAH: anorexigen-induced PAH; WHO FC: World Health Organization functional class; BP: blood pressure; eGFR: estimated glomerular filtration rate; pro-BNP: pro-brain natriuretic peptide; NA: not applicable. #: adjusted only for age; ¶: n=41.

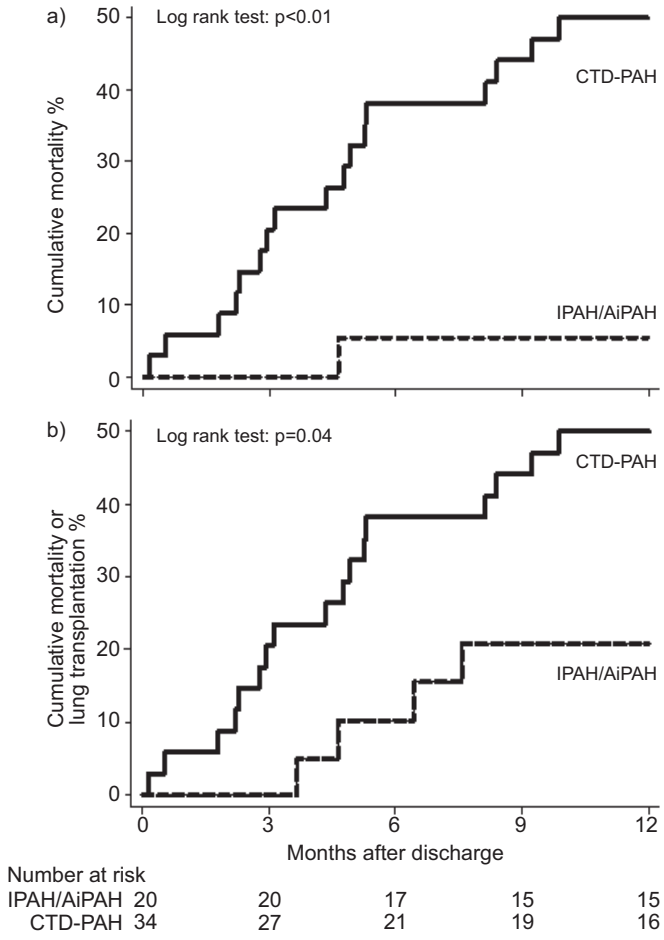


**FIGURE 1.** Outcomes after discharge in patients with right heart failure hospitalisation by underlying diagnosis. a) Mortality after discharge by underlying diagnosis. b) Mortality or lung transplantation after discharge by underlying diagnosis. CTD: connective tissue disease; PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; AiPAH: anorexigen-induced PAH.

p=0.03), and eGFR <60 mL·min$^{-1}$/1.73 m$^2$ at discharge (HR 5.84; p=0.02). After adjusting for age and Charlson comorbidity index, the presence of CTD conferred a HR of 15.3 (95% confidence interval 1.77–133); p=0.01). Regarding parameters obtained upon admission, only eGFR <60 mL·min/1.73 m$^2$ was a significant risk factor for discharge mortality (adjusted HR 5.93 (95% confidence interval 1.68–20.9); p<0.01).

## DISCUSSION

Our study reveals the following important findings relative to patients with PAH who require hospital admission after diagnosis of their disease: 1) RHF is by far the most common reason for hospital admission, and the need for ICU care is not infrequent; 2) in-hospital mortality and mortality after discharge are exceedingly high; and 3) the main prognostic factors of poor outcomes related to RHF hospitalisation include admission hyponatraemia and hypotension, underlying CTD and presence of renal dysfunction.

### *Course and outcomes for RHF hospitalisation*

This study demonstrates a high mortality for patients with RHF requiring hospitalisation, with rates of 14% during hospital admission, and 13, 26 and 35% at 3, 6 and 12 months, respectively, after discharge. These results are in stark contrast with studies of LHF indicating rates of inpatient mortality mostly in the order of 3–5% [12, 15–19], although higher rates of 7 [20] and 9% [21] have been occasionally reported. Mortality after discharge for LHF has been reported at 10.7% at 30 days [21], 10.3% at 60 days [19] and 8.6% at 60–90 days [17].

The clinical characteristics of our patients with PAH were remarkably different from those described in LHF patients. PAH patients are younger and predominantly females, whereas LHF affects males and females equally [12]. PAH patients suffer less frequently from comorbid conditions common in LHF, such as atrial fibrillation, diabetes or systemic hypertension [12, 15, 18, 20, 21]. Additionally, the burden of

**TABLE 4** Risk factors for mortality or lung transplantation within the first year after discharge in patients with first right heart failure hospitalisation

| | Unadjusted HR (95% CI) | p-value | Adjusted for underlying diagnosis and age HR (95% CI) | p-value |
|---|---|---|---|---|
| **Age per year** | 0.99 (0.96–1.02) | 0.40 | NA | |
| **Male *versus* female** | 2.82 (0.82–9.63) | 0.10 | 3.04 (0.80–11.5) | 0.10 |
| **CTD-PAH *versus* IPAH/AiPAH** | 3.04 (1.02–9.05) | 0.04 | 5.66 (1.67–19.2)$^{\#}$ | <0.01 |
| **WHO FC pre-admission** | 4.39 (2.02–9.53) | <0.01 | 3.58 (1.63–7.88) | <0.01 |
| **Charlson index ⩾2** | 3.22 (1.36–7.63) | <0.01 | 2.98 (0.11–8.01) | 0.03 |
| **Use of inotropes during admission** | 2.63 (1.01–6.81) | 0.05 | 2.37 (0.9–6.22) | 0.08 |
| **Haematocrit per %** | 1.01 (0.94–1.08) | 0.76 | 1.04 (0.96–1.12) | 0.32 |
| **Systolic BP ⩽100 mmHg upon admission** | 1.62 (0.54–4.83) | 0.38 | 1.77 (0.58–5.44) | 0.32 |
| **eGFR <60 mL·min$^{-1}$/1.73 m$^2$ upon admission** | 3.58 (1.39–9.25) | <0.01 | 5.93 (1.68–20.9) | <0.01 |
| **Na ⩽136 mEq·mL$^{-1}$ upon admission** | 2.08 (0.88–4.91) | 0.09 | 1.72 (0.71–4.16) | 0.23 |
| **eGFR <60 mL·min$^{-1}$/1.73 m$^2$ at discharge** | 2.75 (1.07–7.1) | 0.04 | 5.84 (1.27–26.7) | 0.02 |
| **Na ⩽136 mEq·mL$^{-1}$ at discharge** | 0.82 (0.35–1.92) | 0.64 | 0.67 (0.26–1.68) | 0.39 |

HR: hazard ratio; NA: not applicable; CTD: connective tissue disease; PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; AiPAH: anorexigen-induced PAH; WHO FC: World Health Organization functional class; BP: blood pressure; eGFR: estimated glomerular filtration rate. $^{\#}$: adjusted only for age.

hospital admission appears higher in RHF compared with studies on acute LHF done in the USA, with longer length of stay [12, 15, 18], and more frequent ICU admissions [15].

### *Hyponatraemia and hypotension on admission are significant prognostic factors for mortality during RHF hospitalisation*

Similar to LHF [18, 21, 22], hyponatraemia and low SBP were strong predictors of mortality during admission. Hyponatraemia portended a four-fold risk of in-hospital mortality. Patients with hyponatraemia were also characterised by other severity indices such as lower SBP, increased heart rate and BUN levels, higher requirement for inotropes or ICU admission and a longer length of stay. Hyponatraemia is a well established prognostic factor in LHF [18, 21, 22], and has been attributed to neurohormonal activation mediated mostly by vasopressin and causing water retention. We have previously demonstrated that hyponatraemia is a strong indicator of poor long-term survival in patients with PAH [5]. In the current cohort, hyponatraemia was strongly associated with low SBP, which was itself a significant predictor for in-hospital mortality, suggesting mediation by neurohormonal activation in the context of low cardiac output. Increased sympathetic activation has recently been demonstrated in PAH and is thought to correlate with disease severity and impact haemodynamics in a similar manner to LHF [23].

Low SBP portended a four-fold increase in in-hospital mortality for patients with SBP <100 mmHg upon admission. Most patients requiring pressure support received dopamine, generally at low dose to ensure renal perfusion, and reflecting a team preference at our institution for this particular vasopressor in the case of RHF. Although no standardised treatment has yet been established for RHF, dopamine has been traditionally used in acute RHF [1, 24], and recommended for nontachycardic patients with hypotension [24], as dobutamine is more likely to cause systemic hypotension. However, dobutamine with or without the addition of norepinephrine has recently been proposed for inotropic support for RHF secondary to PAH [2, 25] due to its ability to restore right ventricular pulmonary arterial coupling and cardiac output with less tachycardic effect [26]. Further studies are warranted to assess the impact of specific vasopressor protocols on altering this particular outcome.

### *Impact of CTD and renal dysfunction on survival*

Patients with CTD-PAH had a five-fold increment in in-hospital mortality, and up to 5.6-fold increased risk of death after discharge compared with IPAH/AiPAH, conferring a 50% mortality at 12 months for CTD-PAH patients. It is now well established that patients with CTD, in particular patients with systemic sclerosis, have a poorer long-term prognosis than patients with IPAH [6, 27]. It has been hypothesised that a particularly inadequate right ventricular adaptation to an increased afterload contributes to rapidly progressive RHF and death [6, 28]. However, the higher prevalence of renal impairment might have conferred an increased risk in patients with CTD-PAH in this study, as we have previously demonstrated in stable CTD-PAH patients [7].

Renal dysfunction defined by eGFR <60 $mL \cdot min^{-1}/1.73\ m^2$ is a common condition in LHF hospitalisations [12, 16, 17, 21], with a prevalence reported in different series of between 29 and 64% [29–31], and is also prevalent in stable patients with PAH (16.7% in a cohort of heterogeneous PAH patients) [32], conferring a higher risk for mortality [32, 33]. In our cohort, renal dysfunction was remarkably high in CTD patients (72%), but also surprisingly common in IPAH/AiPAH (20%). Multiple factors may contribute to renal impairment in PAH, such as low cardiac output, venous congestion, activation of the renin–angiotensin–aldosterone system, hypoxia, and the use of diuretics. Recent studies in patients with cardiac dysfunction have demonstrated the contribution of venous congestion to a significant degree of renal impairment [34], and its correlation with right atrial pressure [19]. Thus, the higher prevalence of renal impairment in PAH patients admitted to the hospital with RHF may not be too surprising. In addition to older age, other factors may account for a higher prevalence of renal impairment in SSc-PAH patients in the absence of scleroderma renal crisis. The prevalence of renal dysfunction in patients with SSc has been reported at 3% [35]; however, renal functional reserve is impaired in 75% of patients with SSc with normal creatinine levels [36], conferring an increased risk for renal dysfunction in this group.

### *Other potential factors affecting prognosis*

Other clinical differences between IPAH/AiPAH and CTD-PAH are worth noting. The use of intravenous prostacyclin was higher in IPAH/AiPAH: 10 (50%) patients with IPAH/AiPAH were discharged on intravenous prostacyclin, compared with only five (14.7%) patients with CTD ($p<0.01$). While the haemodynamic data were not significantly different between the CTD-PAH and IPAH/AiPAH cohorts at baseline, patients in the former group receiving intravenous prostacyclins had more altered haemodynamics compared with their counterpart IPAH/AiPAH patients. Thus, we cannot discard lack of a more intensive therapy approach as a contributing factor for worse prognosis in CTD-PAH patients. Difficulty in handling administration of intravenous treatment due to frequently associated musculoskeletal impairment [37] and greater age have been the underlying reasons for our centre's preference for oral therapy in SSc-PAH patients. In view of these patients' poor prognosis, use of prostacyclin analogues (including the subcutaneous route) should perhaps be considered more carefully in this group. Finally, patients with CTD were less likely than IPAH patients to be suitable candidates for lung transplant due to older age and associated comorbidities. However, even when considering transplantation as a failure outcome, the differences in outcomes persisted (fig. 1b). Our data support the notion that once there is clinical evidence of right ventricular failure, the prognosis for CTD-PAH patients is extremely poor. Whether this is compounded by renal impairment cannot be ascertained given the high prevalence of renal impairment found in this cohort of SSc-PAH patients.

### *Limitations*

Some limitations of this study must be noted. First, we were unable to analyse the effect of treatment on outcomes due to lack of specific treatment protocol. Secondly, we analysed the prognostic value of blood pressure and laboratory parameters on admission, but not their evolution during hospital stay. Thirdly, due to the high proportion of patients with CTD included in the study, the poor outcomes noted during and

after hospitalisation cannot be generalised to other PAH groups. However, both hyponatraemia and low SBP were high predictors for in-hospital mortality after adjusting for PAH diagnosis, and may potentially be applicable to other PAH populations. We were not able to assess these prediction factors in subgroups of PAH due to the limited number of deaths in each group. Renal dysfunction was a predictor for mortality after discharge, but since very few IPAH patients died and renal impairment was less common, we cannot infer any association of renal dysfunction and outcomes for this group. Finally, since the study included hospitalisations at a single centre, generalisability of the results to other institutions or protocols cannot be inferred.

### *Conclusions*

In conclusion, hyponatraemia and low SBP on admission are the main prognostic factors for in-hospital mortality in patients with PAH admitted for RHF. The short-term outcomes after discharge are poor, and remarkably worse in patients with underlying CTD, suggesting that the need for hospitalisation constitutes in itself a poor prognosis in this group. Renal dysfunction may be of particular importance in these patients, perhaps requiring specific attention (*e.g.* kidney protective management with avoidance of nephrotoxic drugs, controlled use of diuretics, or initiation of angiotensin inhibitors) and warranting further studies. Recognition of these ominous factors of mortality in hospitalised PAH patients should alert the clinician and maybe guide therapeutic decisions to avoid emergence of RHF and prompt consideration of timely lung transplantation in appropriate patients. Further studies are also warranted to assess the efficacy of specific therapeutic protocols in patients thus deemed to be at higher risk for mortality.

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## STATEMENT OF INTEREST

A statement of interest for S.C. Mathai can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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